

In the Specification

Please replace the paragraph at page 7, line 25 through page 8, line 8 with the following paragraph:

D<sup>1</sup> As described in the examples, a gene which encodes a cell membrane-associated ligand which is present in the nervous system and the vascular system has been shown to be expressed by arterial endothelial cells and not by venous endothelial cells. Further, the gene which encodes the receptor for the ligand has been shown to be expressed by venous endothelial cells, but not by arterial endothelial cells. Thus, for the first time, an arterial endothelial cell-(artery-)specific marker and a venous endothelial cell-(vein-)specific marker are available, making it possible to distinguish between arteries and veins for a variety of purposes, such as further study and understanding of the mechanisms of blood vessel formation; selective targeting of treatments or therapies to arteries or veins (targeting to arteries but not veins or vice versa) and selective modulation (enhancement or inhibition) of formation, growth and survival of arteries and/or veins.

Please replace the paragraph at page 12, lines 3 through 10 with the following paragraph:

D<sup>2</sup> As used herein, a transgenic mouse is one which has, incorporated into the genome of some or all of its nucleated cells, a genetic alteration which has been introduced into the mouse or at least one of its ancestors, by the manipulations of man. A transgenic mouse can result, for example, from the introduction of DNA into a fertilized mouse ovum or from the introduction of DNA into embryonic stem cells.

Please replace the paragraph at page 16, line 19 through page 17, line 10 with the following paragraph:

D<sup>3</sup> As a result of the work described herein, it is possible to differentiate between arterial endothelial cells (arteries) and venous endothelial cells (veins) by taking advantage of the

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presence of an artery-specific or vein-specific gene product on the surface of the cells. Arterial endothelial cells and venous endothelial cells can each be isolated from cells of other tissue types by, for instance, excision of artery or vein tissue from a sample of mammalian tissue, dissociation of the cells, allowing the cells to bind, under appropriate conditions, to a substance which has some property or characteristic (e.g., a molecule which provides a label or tag, or molecule that has affinity for both an artery-specific cell surface protein and another type of molecule) that facilitates separation of cells bound to the substance from cells not bound to the substance. Separation of the cells can take advantage of the properties of the bound substance. For example, the substance can be an antibody (antiserum, polyclonal or monoclonal) which has been raised against the protein specific to arterial endothelial cells (or to a sufficiently antigenic portion of the protein) and labeled with a fluorochrome, with biotin, or with another label. Separation of cells bound to the substance can be by FACS, for a fluorescent label, by streptavidin affinity column, for a biotin label, by other affinity-based separation methods, or, for example, by antibody-conjugated magnetic beads or solid supports.

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Please replace the paragraph at page 21, lines 7 through 31 with the following paragraph:

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A drug that inhibits interaction of an artery-specific cell surface molecule (e.g., an arterial endothelial cell-specific surface molecule) with a vein-specific cell surface molecule (e.g., a venous endothelial cell-specific surface molecule) can be identified by a method in which, for example, the arterial endothelial cell-specific surface molecule and the venous endothelial cell-specific surface molecule are combined with a drug to be assessed for its ability to inhibit interaction between the cell-specific molecules, under conditions appropriate for interaction between the cell-specific molecules. The cell-specific molecules may be used in the assay such that both are found on intact cells in suspension (e.g., isolated arterial or venous endothelial cells, immortalized cells derived from these, or cells which have been modified to express an artery- or vein-specific cell surface molecule); one cell type is fixed to a solid support, and the other molecule, specific to the other cell type, is in soluble form in a suitable solution; or the molecule specific to one cell type is fixed to a solid support while the molecule specific to the other cell

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Cont type is found free in a solution that allows for interaction of the cell-specific molecules. Other variations are possible to allow for the convenient assessment of the interaction between the two different cell-specific molecules.

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Please replace the paragraph at page 28, lines 1 through 24 with the following paragraph:

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D5 The differential expression of EphrinB2 in arteries and of EphB4 in veins allows for the specific targeting of drugs, diagnostic agents or other substances to the cells of arteries or of veins. A targeting vehicle can be used for the delivery of such a substance. Targeting vehicles which bind specifically to EphrinB2 or to Eph4 can be linked to a substance to be delivered to the cells of arteries or veins, respectively. The linkage can be via one or more covalent bonds, or by high affinity non-covalent bonds. A targeting vehicle can be an antibody, for instance, or other compound which binds either to EphrinB2 or to EphB4 with high specificity. Another example is an aqueously soluble polypeptide having the amino acid sequence of the extracellular domain of EphB4, or a sufficient portion of the extracellular domain (or a polypeptide having an amino acid sequence conferring a similar enough conformation to allow specific binding to EphrinB2), which can be used as a targeting vehicle for delivery of substances to EphrinB2 in arteries. Similarly, a soluble polypeptide having the amino acid sequence of the extracellular domain of EphrinB2 or a sufficient antigenic portion of the extracellular domain (or a polypeptide having an amino acid sequence conferring a similar enough conformation to allow specific binding to EphB4), can be used to target substances to EphB4 in veins.

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Please replace the paragraph at page 38, lines 3 through 11 with the following paragraph:

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D6 Defects in yolk sac angiogenesis were apparent by E9.0 and obvious at E9.5. There was an apparent block to remodeling at the capillary plexus stage, for both arterial vessels, as revealed by  $\beta$ -galactosidase staining, and venous vessels in the anterior region of the sac, as revealed by PECAM staining. Thus, disruption of the EphrinB2 ligand gene caused both a non-

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cont autonomous defect in EphB4 receptor-expressing venous cells, and an autonomous defect in the arteries themselves.

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Please replace the paragraph at page 39, lines 15 through 30 with the following paragraph:

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D7 Similar to the yolk sac phenotype, the capillary bed of the head appeared dilated in the mutant, and apparently arrested at the primary plexus stage. Staining for  $\beta$ -galactosidase revealed that the anterior-most branches of the internal carotid artery failed to develop in the mutant. Unlike the case in the yolk sac, therefore, the malformed capillary beds must be entirely of venous origin. However the anterior branches of the anterior cardinal vein formed although they were slightly dilated. Taken together, these data indicate that in the head, venous angiogenesis is blocked if the normal interaction with arterial capillaries is prevented. The angiogenic defects observed in the head and yolk sac are unlikely to be secondary consequences of heart defects (see below), since they are observed starting at E9.0 and the embryonic blood circulation appears normal until E9.5.

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Please replace the paragraph at page 41, lines 5 through 19 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

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D8 In EphrinB2<sup>lacZ</sup>/EphrinB2<sup>lacZ</sup> embryos, capillary ingrowth into the neural tube failed to occur. Instead, EphrinB2-expressing endothelial cells remained associated with the exterior surface of the developing spinal cord. Comparison of  $\beta$ -galactosidase to pan-endothelial PECAM-1 and EphB4 expression provided no evidence of a separate, venous capillary network expressing EphB4 in the CNS at this early stage (E9-E10). Rather, expression of a different EphrinB2 receptor, Eph B2, was seen in the neural tube as previously reported (Henkemeyer, et al., Oncogene 9:1001-1014 (1994)), where no gross morphological or patterning defects were detectable. In this case, therefore, the mutation does not appear to cause a non-autonomous